**Remarks**

***Amendments to the Claims***

Claims 1-3, 5 and 6 are pending. Claim 1 has been amended to incorporate the limitations of claims 2 and 5. This raises no new issues and cancels issues on appeal. Claim 5 has been amended to depend from claim 1 and to cancel VCAM, ICAM, CD44, and $V_3V_X$, thereby narrowing issues on appeal and raises no new issues. Claim 2 is now dependent on claim 1 and is specific to the cancelled material from claim 5. Claim 6 has been amended to depend from the amended claim 1. These amendments should be entered. Claim 5 is believed to be allowable in view of the examiner's remarks in the office action.

***The Claimed Invention***

The claims are drawn to isolated active osteopontin peptide fragments that have cell-attachment and cell-spread activity (page 7, line 23 to page 8, line 12). The peptide fragments may be coated on a material in order increase cell attachment to the material, as well as enhance cell spread (page 9, lines 27-29). The material is suitable for use *in vivo* and is capable of being part of an implant (page 10, lines 16-23), such as a dental or an orthopedic implant (page 14, lines 24-28).

Independent claim 1 defines active osteopontin peptide fragment comprising an amino acid sequence selected from the group consisting of SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, and SEQ ID NO:15 (see at least page 8, lines 7-26 and page 12, lines 4-13) , wherein the peptide binds to at least one integrin receptor on a cell surface.

Dependent claim 2 defines the active peptide fragment of claim 1, wherein the peptide increases cell attachment to a material and increases cell spread (see at least page 8, lines 11-12 and page 53, lines 12-17).

Dependent claims 3 and 5 define the active peptide fragment of claim 1, wherein the integrin(s) is $\alpha_v\beta_3$, $\alpha_v\beta_5$, $4\beta_1$, and $2\beta_1$ OR VCAM, ICAM CD44, or $V_3V_x$. Support for claims 3 and 5 can be found at least on page 3, line 27 to page 4, line 14 and page 53, lines 17-21.

Dependent claim 6 defines the active peptide fragment of claim 1, wherein the cell is an osteoprogenitor cell, tumor cell, macrophage, periosteal cell, endothelial cell, epithelial cell, eosinophil, stem cell, limited potential precursor cell, precursor cells committed precursor cell, or differentiated cell (see at least page 8, line 29 to page 9, line 2).

The claims are directed to active osteopontin peptide fragments and their use in and/or on materials to increase cell attachment and cell spread activity. The peptide fragments comprise the sequences VFTPVVPTVDTYDGRGDSVVYGLRSKSKKFRRP (SEQ ID NO. 7), RSRRATEVFTPVVPTVDTYDGRGDSVVYGLRSKSKKFRRP (SEQ ID NO:8), SDELVTDFPTDLPATEVFTPVVPTVDTYDGRGDSVVYGLRSKSKKFRRP (SEQ ID NO:9), RSRRATEVFTPVVPTVDTYDGRGDSVVYGRRSKSKKFRRP (SEQ ID NO:10), RSRRATEVFTPVVPTVDTYDGRGDSVVYGRRSKSKKFRRPAGAAGGPAGPAG PAGPAGPAGPA (SEQ ID NO:11), RSRRVFTPFIPTESANDGRGDSVAYGLKSKSKKFRR (SEQ ID NO:12), DTFTPIVPTVDVPNGRFDSLAYGLKSKSKKFQ (SEQ ID NO:13), RSRRATEVFTPVVPTVDTYDGRADSVVYGRRSKSKKFRRP (SEQ ID NO:14), and acetyl-RSRRATEVFTPVVPTVDTYDGRGDSVVYGLRSKSKKFRRP (SEQ ID NO:15).

The peptides may be used to coat a material suitable for use *in vivo* (producing an active osteopontin peptide fragment-coated implant), in order to increase cell binding to the implant and increase cell spread. The active osteopontin peptide fragments increase cell binding and spread by binding to at least one integrin receptor, such as $\alpha_v\beta_3$, $\alpha_v\beta_5$, $4\beta_1$, $2\beta_1$, VCAM, ICAM CD44, $V_3V_x$, on the surface of cells. The peptide fragments may be used to increase attachment and spread of a number of different cell types, including osteoprogenitor cells, tumor cells, macrophages, periosteal cells, endothelial cells, epithelial cells, eosinophils, stem cells, limited potential precursor cells, precursor cells, committed precursor cells, and differentiated cells.

**Rejection of claims 1-3, 5 and 6 Under 35 U.S.C. § 112, first paragraph, enablement**

***The Legal Standard for Enablement***

Whether the disclosure is enabling is a legal conclusion based upon several underlying factual inquiries. See *In re Wands*, 858 F.2d 731, 735, 736-737, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir.1988). As set forth in *Wands*, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. In cases that involve unpredictable factors, "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive.' *Atlas Powder Co., v. E.I. DuPont De Nemours & Co.* , 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir.1984). There is no requirement for

examples. The Supreme Court also noted that all of the factors need not be reviewed when determining whether a disclosure is enabling *In re Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (noting that the *Wands* factors 'are illustrative, not mandatory. What is relevant depends on the facts.'). As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. *In re Douglas v. United States* 510 F.2d 364; 184 U.S.P.Q. 613 (Ct. Cl.1975) the Court of Claims noted that a patentee cannot "be expected to foresee every technological problem that may be encountered in adapting his idea to a particular use. Some experimentation and exercise of judgment is to be expected. *In re Mineral Separation v. Hyde* 242 U.S. (1916), the court emphasized that some inventions cannot be practiced without adjustments being made to adapt them to the particular context. In such a situation, a specification is sufficient if it gives adequate guidance to one skilled in the art on how such adjustments are to be made.

***Analysis***

The claims are directed to active osteopontin peptide fragments comprising SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, or SEQ ID NO:15. The amino acid sequences of the peptides are disclosed (page 8, lines 7-26), and the specification on page 11, lines 9-11 and on page 12, lines 20-31 to page 13, lines 1-5, discloses how osteopontin can be modified to obtain the claimed peptides. The structure of osteopontin is well known in the art. It would therefore be routine for one skilled in the art to make the claimed peptides from the known structure of osteopontin, or, with knowledge of the disclosed sequences using other well known synthetic techniques.

Therefore claim 1 which recites active osteopontin fragments with disclosed amino acid sequences is enabled.

The peptides may be used to increase cell attachment to a biomaterial and to increase cell spread. The specification on page 13, line 14 to page 14, line 2 describes how to coat the peptides onto a material, and the types of materials that may be coated (page 10, lines 16-23 and page 14, lines 22-28). The specification on page 40, lines 4-31, and page 41, lines 1-8, describes how to measure cell attachment and cell spread. Therefore, it is clear that claim 2, which recites that the peptide increases cell attachment to a material and increases cell spread is enabled.

An active osteopontin peptide refers to an osteopontin fragment that possesses at least one biological activity of naturally occurring osteopontin (see page 11, lines 9-11). The biological activity of osteopontin that the claimed peptides have includes cell attachment and cell spread activity. Osteopontin performs these biological functions by bindings to its receptors on the cell surface. As stated in the specification on page 3, line 27 to page 4, lines 1-14, these peptides bind to integrins as demonstrated by the ability of anti-integrin antibodies to inhibit cell attachment and cell spread induced by the peptides (for example, SEQ ID NO: 15, (Example 12 and Table 8)). Although there is no need for examples, this example clearly demonstrates that the claimed peptides do indeed bind to integrins. The specification provides guidance on how to identify the integrin involved in increased cell binding and cell spread induced by the claimed peptides. The specification enables one to culture plates with any type of cell expressing different receptor/integrin molecules, and assay for cell attachment and/or cell spread in the presence or absence of the claimed peptides. The percent increase in cell attachment and cell spread are readily measured by methods commonly used in the art. Antibodies to different integrins, such as those recited in claims 3 and 5 ($\alpha_V\beta_3$, $\alpha_V\beta_5$, $4\beta_1$, $2\beta_1$, VCAM, ICAM CD44,

$V_3V_x$) can then be employed determine if the increase in cell binding/cell spread is attenuated, and thereby identify the integrin required for the observed increase in cell binding/cell spread. Anti-integrin antibodies may be produced or obtained from many commercial suppliers. Applicants have demonstrated the attenuation of osteopontin peptide-induced binding in the presence of anti-$\alpha_v\beta_3$ in osteoprogenotir cells, demonstrating binding to $\alpha_v\beta_3$ integrin.

Accordingly, although some experimentation is required to determine which integrin is involved in the increase in binding and cell spread observed in response to the claimed peptides, the experimentation is not undue, there is clear guidance in the specification on how to perform the assays (which are also routinely performed in the art), and there are working examples in the specification. There is no legal requirement that the claimed peptides bind all integrins or to all cell types for the peptides to have the specified utility. There is no legal requirement for actual reduction to practice. Claim 2 which recites that the active osteopontin peptides increase cell attachment to a biomaterial and increases cell spread by binding to at least one integrin receptor on the cell surface, and claims 3 and 5 which recite that the peptides increases cell attachment to a biomaterial and cell spread by binding to an integrin selected from a group consisting of $\alpha v\beta 3$, $\alpha v\beta 5$, $4\beta 1$, $2\beta 1$, VCAM, ICAM CD44, V3Vx are therefore enabled.

Integrins are the principal receptors on animal cells for binding most extracellular matrix proteins, including collagen, fibronectin, and laminin. They are found on the surface of numerous cell types (see, for example, *Molecular Biology of the Cell*. IV. Cells in Their Social Context. 19. Cell Junctions, Cell Adhesion, and the Extracellular Matrix, Garland Publishing (1994)). Since integrins are expressed on diverse cell types, it would be expected that the claimed peptides would bind the diverse cell types expressing integrins. The specification

describes a number of cell types that may be regulated using the active osteopontin peptides fragments (page 8, line 29 to page 9, line 2). Although there is no requirement for examples, Example 12 and Table 8 on pages 53-55, demonstrate that plates coated with each of, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14 or SEQ ID NO:15 binds to osteoprogenitor cells and significantly increases cellular attachment and spread over the control (uncoated plates). There are art recognized techniques for determining the integrin expression profile of a cell, and the integrins expressed by the cells recited in claim 6 are known in the art. Because of the ubiquitous expression of integrins on cells, and the fact that the specification clearly demonstrates the ability of the peptides to increase attachment to a biomaterial and cell spread, as well as the ability of the peptides to bind to at least one integrin receptor on the cell surface, claim 6 which defines the use of the claimed peptides to increase cell attachment and spread to the cell types recited in the claim, wherein the peptide binds to at least one integrin receptor is enabled.

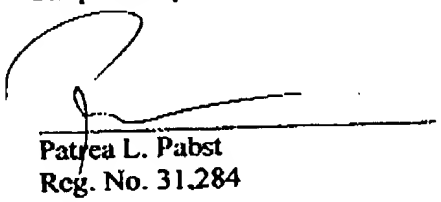
In response to the examiner's statements regarding Hu, et al., Hu, et al., is not evidence that osteopontin does not bind the integrins of claim 3 as amended, nor that other cell types than osteoclasts do not have integrins bound by the claimed peptides. No evidence in support of the examiner's position has been provided, only argument.

The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir.1988). It is clear from the direction or guidance given by the specification, the presence of working examples, the state of the prior art and the relative skill of those in the art, that one of

ordinary skill in the art could make and use the claimed osteopontin-derived peptide fragments to increase cell attachment to a material.

Allowance of claims 1-3, 5 and 6 is earnestly solicited.

Respectfully submitted,



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